

Investigation of hepatitis B virus prevalence and reactivation frequency in malignancy patients administering chemotherapy

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Abstract

Aim: This study aimed to investigate the frequency at which physicians test hepatitis B virus (HBV) serology before treatment and the rate of hepatitis B virus reactivation (HBVr) after treatment in patients undergoing chemotherapy (CT) due to a solid organ malignancy (SOM) or hematological malignancy (HM).

Materials and Methods: Baseline clinical feature, HBV serology, and liver function test data for 1275 patients \geq 18 years of age who underwent CT for the first time due to various SOMs and HMs from 2015-2017 were obtained from the database and retrospectively analyzed. HBV serology was studied in 296 (201 HM, 95 SOM) of the 1275 patients retrieved from the database.

Results: The prevalence of HBV was 9.5% (121 patients). Only 49 (40.4%) HBV-positive patients had HBV DNA. Of those, 72 (59.5%) underwent prophylactic antiviral therapy. HBVr was detected in only 3 patients (1.5%), and all of those patients had HMs and were recommended oral antiviral therapy but did not.

Conclusion: In patients with SOMs, the screening rates of HBV serology, as well as prophylaxis and follow-up HMs were extremely low. Therefore, these patients should be screened for HBV serology and prophylactic treatment should be given when necessary for HBVr.

Keywords: Chemotherapy; Hepatitis B; reactivation; screening

INTRODUCTION

An estimated 2 billion people globally are infected with the hepatitis B virus (HBV) and 1/8 of it is a chronic transporter. About 15% to 25% of these infected patients also die from cirrhosis or hepatocellular cancer (HCC) (1,2). The overall prevalence of the hepatitis B surface antigen (HBsAg) varies depending upon the geographic area. High-prevalence areas include the Asia-Pacific area, and the HBV range is \geq 8 percent (3,4).

The progression of HBV infection depends on the outcome of the interaction between viral replication and the host's immune system. HBV persists in the body of all infected patients, even those with evidence of serological recovery. Therefore, patients infected with HBV are at serious risk of hepatitis B reactivation (HBVr) during immunosuppressive therapy (5). Clinical results vary from only asymptomatic with the elevation of liver enzymes to serious hepatitis and fatality. In addition to causing liver injury, HBVr may also

endanger the patient's health by delaying chemotherapy or early termination (6). It is well known that HBVr may progress after immunosuppressive therapy and can be prevented by prophylactic treatment given in advance of the therapy. Although the definition of HBVr varies in the literature, the goal is to prevent the development of acute liver failure or decompensation (7).

HBVr was found in patients who experienced chemotherapy for the treatment of various solid and hematological tumors (8). Most evidence has shown that hematological malignancies, especially lymphomas, have observed a significant liver failure and mortality rate following HBVr in both HBsAg positive and occult HBV infection patients (9, 10). Most studies have also shown that patients who underwent HBV screening and prophylaxis treatment before CT sessions had obviously diminished HBVr proportions and associated death rate (11,12). However, this situation has been much less explored in patients with solid organ malignancy (SOM) (6).

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Several aspects of HBVr prevention remain unclear. In recent years, it has been recognized that HBVr can be efficiently prevented by following chemotherapy with antiviral prophylactic therapy. However, there is no clear approach to HBV prophylaxis with therapeutic agents. If prophylaxis is given, there is no consensus about the imaging frequency during the prophylaxis process. The duration and preferred type(s) of prophylaxis are unknown. Early studies of HBVr were disrupted due to the absence of a consensus in the case definition and the insensitivity to the methods used to measure viral replication (13).

Most hepatologist guidelines recommend HBsAg screening and antiviral prophylaxis prior to CT sessions for patients with indications (14-16). While this situation is definite for all hematological malignancy (HM) patients, it is not definite for SOM patients. This difference suggests screening occurs only in high-risk patients, due to the limited evidence of HBVr in SOM patients and their immunosuppression level being lower than in HM patients.

In this study, the aim was to adjust HBsAg screening rates, HBV prevalence, and HBVr frequency in both SOM and HM patients before CT.

MATERIALS and METHODS

The characteristics of the participants

The reviewed data is from the registration database of the Hematology and Medical Oncology units of Malatya Inonu University Turgut Ozal Medical Center, which is a tertiary health institution. A total of 1275 patient files were retrospectively evaluated in accordance with the Helsinki Declaration decisions, patient rights regulations, and ethical rules with approval from the Malatya Clinical Research Ethics Committee (Approval number: 2017/21-1). The following inclusion criteria were used for all reviewed medical records included in the study: 1) 18 years old or over HM and SOM patient with CT performed at Turgut Ozal Medical Center between 01/01/2015 and 03/15/2017 and 2) the patient was followed at least 6 months after the first CT session was stopped or until death. Patients from other hospitals who had previously undergone CT and had no initial HBV serology test were excluded. Patients who received IFN- α 2B due to renal malignant neoplasm and patients to whom abiraterone therapy was administered for prostate malignant neoplasm were excluded from the study.

Data screening

The baseline data of patients—including age, gender, primary tumor, chemotherapy protocol, aspartate aminotransferase (AST) level, alanine transaminase (ALT) level, and pre-chemotherapy HBV serology (HBsAg, anti-HBs, anti-HBc total, HBeAg, and anti-HBe)—were screened from the hospital computer registration database. If patients were positive for HBsAg, we investigated whether patient HBV DNA was tested before CT and whether patient received antiviral prophylaxis. Patients whose HBV serologies were available were divided into groups (HBV-sensitive, acute infection, chronic HBV infection, previous infection, isolated anti-HBc positivity) according to their

HBV status. Patients who were at risk for HBVr (patients who had chronic infection, previous infection, only anti-HBc positivity) were evaluated in terms of their AST, ALT parameters, and HBV DNA levels.

Description of expressions

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HBV screening: HBsAg was checked in the blood at any time before CT.

HBV infection: All patients who are positive for the HBsAg test.

Hepatitis: Expressed as an enhancement of the serum ALT level by three-fold or more than the normal upper cutoff value (>40 IU/L) or an absolute enhancement of the ALT level above 100 IU/L (17).

HBV reactivation: HBV DNA levels were expressed 10-fold or more compared to initial value or positive (>1,000 \times 10⁶ genome equivalents/mL) in patients with previously negative HBV DNA (13).

Statistical Analysis

In the data evaluation process, the data was divided based on median values (min-max) and number values (%). The Kolmogorov-Smirnov test was performed for normal distribution values. The Pearson chi-square test was used for statistical analysis. The results were evaluated using a 95% confidence interval and a 5% significance level (p -value = <0.05). IBM SPSS Statistics 22.0 program was used for statistical analysis.

RESULTS

Characteristics of patients participating in the study

In the 3-year study period, 655 of the patients evaluated were male, and 620 were female. The average age of the patients was 58 (age range of 17–94). Of the 1275 patients who received chemotherapy for the first time due to solid organ and hematological malignancies, 1,032 were diagnosed with solid organ malignancies and 243 with hematological malignancies (Figure 1). The Number of Patients Included in the Study with a Diagnosis of Solid Organ and Hematological Malignancy was determined in detail. (Figures 2 and 3).

While only HBsAg was studied before chemotherapy in 14 of these patients (HM 9/243, SOM 5/1032 1.09%), HBsAg and anti-HBc were studied in 3 patients (HM, 0/243; SOM 3 / 1032; total 3/1275, 0.23 %). However, in 279 patients (HM: 192/243; SOM: 87/1032; total 279/1275, 21.8%) HBsAg, Anti-HBc Total and Anti-HBs were screened together, and finally, as HBV serology, 296/1275 (23.1%) patients were examined (Table 1).

HBV screening and management

The greater majority of the 296 patients suffered from hematological malignancies. Of the 243 HM patients, 201 (82.7%) were screened for HBV serology. From the medical oncology SOM patients, only 95 (9.2%) were screened with regard to HBV serology (Table 1).

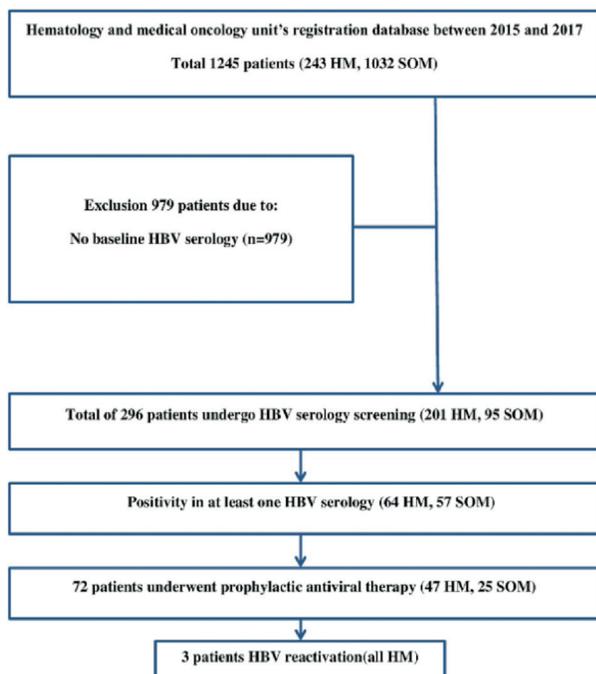


Figure 1. The study population obtained in the registration database

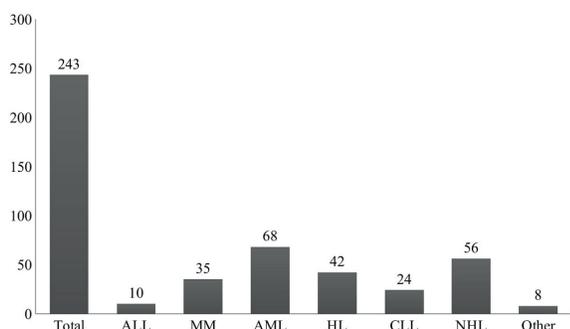


Figure 2. Number of patients included in the study with the diagnosis of hematological malignancy

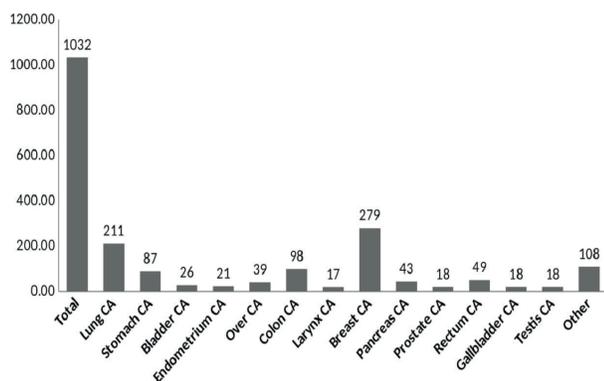


Figure 3. Number of patients included in the study with the diagnosis of solid organ malignancy

Prior to chemotherapy, the number of HBV DNA studies in the patients with positive HBV serology was found to be low. Only 49 (40.4%) of the 121 patients whose HBV serology was determined to be positive were later evaluated for HBV DNA positivity. When this data was

screened in detail, the HM patient group appeared to have been screened in more detail, compared to the SOM patients (Table 3).

Table 1. The number of the patients who underwent HBV screening before Chemotherapy and the type of the screening methods

Groups	HBsAg Positive n(%)	HBsAg and Anti-HBc Total Positive n(%)	HBsAg, Anti-HBc Total and Anti-HBs Positive n(%)	Total n(%)
Hematological Malignancy	9/243 (3.7)	0/243 (0)	192/243 (79)	201/243 (82.79)
Solid Organ Malignancy	5/1.032 (0.48)	3/1.032 (0.29)	87/1.032 (8.4)	95/1.032 (9.17)
All Patients	14/1.275 (1.09)	3/1.275 (0.23)	279/1.275 (21.8)	296/1.275 (23.12)

Table 2. HBsAg and Isolated Anti-HBc Total Positive Patient Rates in Patients Screened for HBV Serology Before Chemotherapy

Groups	HBsAg Positive n(%)	Isolated Anti-HBc Total Positive n(%)	HBsAg, Anti-HBc Total and Anti-HBs Positive n(%)	Total n(%)
Hematological Malignancy	11/201 (5.4)	15/201 (7.4)	38/201 (18.9)	64/201 (31.7)
Solid Organ Malignancy	18/95 (18.9)	9/95 (9.4)	30/95 (31.5)	57/95 (59.8)
All Patients	29/296 (9.7)	24/296 (8.1)	68/296 (22.9)	121/296 (40.7)

Table 3. HBV DNA Screening Rates in Patients with HBsAg, Isolated Anti-HBc Total and HBsAg, Anti-HBc Total and Anti-HBs Positive before Chemotherapy

Groups	HBsAg Positive n(%)	Isolated Anti-HBc Total Positive n(%)	HBsAg, Anti-HBc Total and Anti-HBs Positive n(%)	Total n(%)
Hematological Malignancy	10/11 (90.9)	4/15 (26.6)	13/38 (34.2)	27/64 (42.1)
Solid Organ Malignancy	16/18 (88.8)	3/9 (33.3)	3/30 (10)	22/57 (38.5)
All Patients	26/29 (89.6)	7/24 (29.1)	16/68 (23.5)	49/121 (40.4)

Among the total 121 HM and SOM patients where HBsAg, isolated anti-HBc total, anti-HBc total, and anti-HBs were jointly positive, 72 (59.5%) were found to administer antiviral prophylactic therapy (Table 4).

Table 4. Prophylactic Antiviral Treatment Rates in Patients Screened for Hepatitis B Virus Reactivation

Groups	HBsAg Positive n(%)	Isolated Anti-HBc Total Positive n(%)	HBsAg, Anti-HBc Total and Anti-HBs Positive n(%)	Total n(%)
Hematological Malignancy	11/11 (100)	8/15 (53.3)	28/38 (73.6)	47/64 (73.4)
Solid Organ Malignancy	16/18 (88.8)	3/9 (33.3)	6/30 (20)	25/57 (43.8)
All Patients	27/29 (93.1)	11/24 (45.8)	34/68 (55.8)	72/121 (59.5)

HBV reactivation

Among the 121 patients whose HBV serology was screened (the groups where HBsAg, isolated anti-HBc total, anti-HBc total, and anti-HBs were jointly positive) only 3 patients (3/121, 2.48%) experienced HBVr, but ALL 3 were HM patients (Table 5). The HBV of these patients had been serologically positive and prophylactic antiviral therapy had been recommended, but the patients had not received it for various reasons.

Table 5. Hepatitis B Virus Reactivation Rates

Groups	HBsAg Positive n(%)	Isolated Anti-HBc Total Positive n(%)	HBsAg, Anti-HBc Total and Anti-HBs Positive n(%)	Total n(%)
Hematological Malignancy	1/11 (9.09)	1/15 (6.6)	1/38 (2.6)	3/64 (4.6)
Solid Organ Malignancy	0/18 (0)	0/9 (0)	0/30 (0)	0/57 (0)
All Patients	1/29 (3.4)	1/24 (4.1)	1/68 (1.4)	3/121 (2.4)

One of the patients who developed reactivation was a 71-year-old male who was diagnosed with myelodysplastic syndrome (MDS). At initiation of chemotherapy, only the patient's anti-HBc total was found to be positive, while his HBsAg and HBV DNA were both negative. After receiving azacitidine treatment for 6 months, the MDS transformed to acute myeloid leukemia (AML), and he received

idarubicin and cytarabine treatment. After a month of that treatment, the patient's HBsAg values became positive. No increase was observed in the patient's AST and ALT values.

Another patient who developed reactivation was a 56-year-old male being followed for AML. The patient received idarubicin and cytarabine treatment. Two months after completion of treatment, the patient received allogeneic hematopoietic stem cell transplantation. He was administered cyclosporine as an immunosuppressive treatment. The patient's pre-chemotherapy anti-HBs and anti-HBc total value were found to be positive, while his HBV DNA value was found to be negative. One year after stem cell transplantation, the patient's HBsAg and HBV DNA parameters became positive, while anti-HBs had turned negative. The patient's AST and ALT values were elevated up to 10 times above the normal upper limit. This patient was prescribed tenofovir at initiation of chemotherapy, but he refused to use it. Later, the patient was again prescribed tenofovir and took it as prescribed. Seven months later, the patient's HBV DNA level became negative again.

Another patient who developed reactivation was a 25-year-old male being followed for relapsed Hodgkin's lymphoma. The patient's pre-chemotherapy HBsAg and anti-HBc total value were positive, while anti-HBs and the HBV DNA value were negative. The patient underwent an autologous hematopoietic stem cell transplant 4 months after administration of cisplatin, cytarabine, and dexamethasone. Four months after stem cell transplantation, the patient's HBV DNA value was found to be positive. His AST and ALT values were 50 times above the normal upper limits.

DISCUSSION

HBV infection is a global public health matter (18). The natural course of the virus is the result of the coaction between viral replication and the host's immune response. Even if the serologic markers of the virus are completely reversed, the infection continues to exist in the hepatocyte nucleoside in all patients (19).

People who administer cytotoxic or immunosuppressive therapy by ASCO are recommended to undergo a serological test. With such tests, it is recommended to look at HBsAg, anti-HBc, and anti-HBs as infection markers. The guidelines expressed that prophylactic antiviral therapy could prevent HBVr in HBsAg-positive individuals. In addition, the guidelines state that HbsAg-positive patients should be treated because of the increased risk of fulminant hepatitis in chronically infected individuals after the start of suppressive therapy and the high risk of reactivation in those who have recovered from the infection. And it is emphasized that anti-HBc-positive liver disease symptoms should be monitored closely (20). Although most guidelines (16, 20, 21) recommend HBV screening in such patients, the rate was particularly low in SOM patients since only 95/1032

(9.2%) had serological tests before CT. Three parameters (HBsAg, anti-HBc, anti-HBsAg) were studied in 30/95 (31.6%). These rates were also much higher, at about 82.8% (201/243), in HM patients. The HBV screening rate among all patients was 23.2% (296/1275). This result is compatible with other studies; the screening of patients was found to be 9.7–10.1% in the study conducted by the Mayo Clinic group (22), and was only 3.9–6.2% in a retrospective study by Jessica P. Hwang et al. at the MD Anderson Cancer Center (23). When we examined patient records, we found that most patients were not screened for HBV parameters. An important point that should be emphasized is the necessity of screening HBV markers at the time of referral. Besides the direct damages caused by HBVr and delayed or terminated chemotherapy, there are also indirect damages, such as patients experiencing a delay in treatment or the inability to access the treatments needed (21). HBV serological tests should include anti-HBc and HBsAg tests. Anti-HBs, however, is not routinely monitored as it is not used to indicate the necessity for prophylaxis (21).

HBVr leads to a wide range of clinical conditions, such as increased transaminase levels, fulminant hepatitis, and/or death. In a previous study, approximately 20–50% of HBVr in chronic hepatitis B infection or HBV-infected individuals receiving immunosuppressed therapy has been shown (23). Because HBV DNA level was not routinely tested within the indication in all patients, we could not determine the true HBVr rate because HBV screenings were performed for only 49 (27 HM, 22 SOM)/121 (40.4%) patients with positive HBV serology. We found that HBVr occurred in 3 patients (2.48%). Before the CT session, all of them were screened for HbsAg; 3 patients were recommended antiviral prophylaxis, but only 2 patients received it. None of them had liver failure or death. However, the fact that the majority of patients were not screened and that their data were followed for only 6 months after the first CT session led to the misconception that HBVr cases were low. However, if we estimate that a total of 40.7% of 979 patients (SOM 90.8%, HM 17.2%) who were not screened for HBsAg were HbsAg positive, we would find a higher HBVr rate. As a result, the prevalence of HBV infection in SOM patients who underwent CT in the current study was 5.5% (57/1032), similar to the rates in previous studies (24).

In a prospective study by Yeo et al., 626 successive cancer patients who received cytotoxic chemotherapy for 12 months were screened for HbsAg, and 78 patients (12%) were HBsAg positive. HBVr was noticed in 15 (19.2%) of 78 patients. HBVr was found to be higher in male, younger age, HBeAg seropositive, and lymphoma patients. To conclude, in this study, HBVr was found to be approximately 20% in patients with CHD infection under chemotherapy (17). In our study, all patients who experienced reactivation were male. This result supports the argument that HBVr is common in men. One of these patients was a young male patient with CHD infection followed by lymphoma, and the risk of HBVr may have been due to the chemotherapeutics given for treatment in lymphoma patients.

In the study of Hsu C et al., HbsAg-negative and anti-HBc-positive lymphoma patients with HBV infection were prospectively observed. HBV DNA was tested at the start of each chemotherapy cycle and then retested every 4 weeks for 1 year after the completion of R-CHOP chemotherapy. Patients diagnosed with HBVr were treated with entecavir for 48 weeks. HBVr and HBV-related exacerbation incidences were determined as 10.4% and 6.4%, respectively. Despite entecavir therapy, 4 patients had severe HBV-related hepatitis. In this study, in HbsAg-negative and anti-HBc-positive lymphoma patients, chemotherapy-induced HBVr was not uncommon, but regular HBV DNA monitoring and antiviral therapy were required. Further, HBsAg reappearance was the most significant predictor of HBV-related hepatitis exacerbation, and it was emphasized (25). In our study, exacerbation developed in 2 of 3 patients who developed HBVr. In Hsu C et al.'s study, the rate of exacerbation development in patients with HBVr was found to be approximately the same as our study.

In our study, in 32 SOM patients followed for risk of HBVr, no reactivation occurred. But reactivation occurred in 3 (17.6%) of 17 HM patients. Among all patients who did not receive antiviral treatment, 3 (6.12%) of 49 patients developed reactivation. One patient who had reactivation was treated only with antiHBctotal positive and chemotherapy, while the other was administered chemotherapy due to an HBV infection and allogeneic bone marrow transplantation. Another patient had CHD infection and had received chemotherapy and autologous bone marrow transplantation.

Finally, in patients with solid organ and hematological malignancies, HBV serology should be screened to determine risk of HBVr prior to starting chemotherapy, and patients should then be subsequently monitored for reactivation. Prophylaxis for HBV infection should be initiated according to the risk score. For each patient who will receive immunosuppressive therapy and chemotherapy, HbsAg and anti-HBc IgG should be checked, and if they are found to be positive, HBV DNA should be checked. Patients in the low-risk group who are not given prophylaxis for reactivation should be monitored for reactivation.

CONCLUSION

According to the studies performed, pre-chemotherapy HBV serology screening rates are low in SOM and HM patient groups. Despite the low screening rate, when reactivation rates are taken into consideration in these patients, antiviral treatment should be started in serologically positive patients. For this reason, chemotherapy and immunosuppressive and biologic therapy should be in close working relationship with doctors. Joint training meetings and programs that raise awareness of HBV should be organized.

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